PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ANTBH/P31763PC	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/GB2005/000007	International filing date *(day/month/year)* 05.01.2005	Priority date *(day/month/year)* 05.01.2004
International Patent Classification (IPC) or national classification and IPC INV. C12N15/62 A61K47/48 C07K14/54 C07K16/30 A61P35/00		
Applicant EMD LEXIGEN RESEARCH CENTER CORP. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 13 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 6 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.12.2005	18.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Dullaart, A Telephone No. +31 70 340-3290

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/000007

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-63	as originally filed
Claims, Numbers	
1-52	received on 12.12.2005 with letter of 09.12.2005
Drawings, Sheets	
1/12-12/12	as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 51-52, and part of 47

because:

☒ the said international application, or the said claims Nos. 47 in part relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☒ no international search report has been established for the said claims Nos. 51-52

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/000007

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has, within the applicable time limit:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest and, where applicable, the protest fee.

   ☐ paid additional fees under protest but the applicable protest fee was not paid.

   ☐ neither restricted the claims nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-50 .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-50
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-50
Industrial applicability (IA)	Yes:	Claims	1-46,48-50
	No:	Claims	47

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ on paper

   ☒ in electronic form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed

   ☐ filed together with the international application in electronic form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment* on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 51 and 52 do not contain any technical features which allow for a search to be performed. The following is limited accordingly.

Claim 47 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

The problem underlying the present application is, to provide an effective medicament for treating solid tumours, and means (i.e., nucleic acids or expression vectors) for their production.
As solution to this problem, several proteins are proposed, in which (part of) interleukin-12 (IL-12) is fused to (part of) an antibody, which targets oncofoetal fibronectin.
The technical feature, linking these solutions together, is the combination of both these features in one single fusion protein, used in the treatment of solid tumours.

However, three documents disclose a fusion protein of anti-oncofoetal fibronectin with IL-12, and its efficacy in the treatment of tumours:
CANCER RESEARCH, vol. 63, no. 12, 15 June 2003 (2003-06-15), pages 3202-3210, ISSN: 0008-5472
CANCER RESEARCH, vol. 63, no. 5, 1 March 2003 (2003-03-01), pages 1144-1147, ISSN: 0008-5472
and
NATURE BIOTECHNOLOGY, vol. 20, no. 3, March 2002 (2002-03), pages 264-269, ISSN: 1087-0156
Moreover, in **WO 03/093478 A**, on page 26, line 24 of the table, the combination IL-12 + anti-oncofetal fibronectin is mentioned as one of the preferred combinations.

For this reason, the technical feature mentioned above can no longer be accepted as special technical feature linking the different inventions together.

The presently claimed fusion proteins can be distinguished from this prior art by the fact, that a different region of the oncofoetal fibronectin is now targeted. Yet, these presently claimed fusion proteins seem to be mere alternative solutions to the problem mentioned above, which was also solved by these previously described fusion proteins.
The fact, that the presently claimed antibody fragment of the fusion protein now should target a different region of oncofoetal fibronectin than ED-B can therefore not fulfil the role of special technical feature in the sense of Rule 13.2 PCT either.

Since there is no other technical feature that could fulfil the role of special technical feature in the sense of Rule 13.2 PCT, the present application is found to lack unity of invention. In principle, each of the fusion proteins falling under the scope of the claims would represent a separate invention. Nevertheless, as the search for each of these subjects seemed complete, and as the reasoning for each of these inventions is based on similar considerations, the present authority decided not to ask for further fees.
Also, it seemed more logical to regroup the inventions in view of the different entities claimed, i.e., fusion proteins, nucleic acids and expression vectors, thus arriving at the subjects mentioned below.

No.	Claims	Subject
1	1-34, 43-50	Compound containing of a portion targeting oncofoetal fibronectin and IL-12 as effector portion, pharmaceutical composition containing it, and its use in the treatment of cancer, according to these claims.
2	35-39	Nucleic acid encoding the fusion protein of anti-oncofoetal fibronectin and IL-12, or encoding part of it.
3	40-42	Expression vector as claimed, host cell as claimed, and their use in the method of making a compound as claimed

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:

D1: HALIN CORNELIA ET AL: "Synergistic therapeutic effects of a tumor targeting antibody fragment, fused to interleukin 12 and to tumor necrosis factor alpha." CANCER RESEARCH, vol. 63, no. 12, 15 June 2003 (2003-06-15), pages 3202-3210, XP002342601 ISSN: 0008-5472

D2: THORPE P E ET AL: "The First International Conference on Vascular Targeting: Meeting overview" CANCER RESEARCH 01 MAR 2003 UNITED STATES, vol. 63, no. 5, 1 March 2003 (2003-03-01), pages 1144-1147, XP002342602 ISSN: 0008-5472

D3: HALIN C ET AL: "Enhancement of the antitumor activity of interleukin-12 by targeted delivery to neovasculature" NATURE BIOTECHNOLOGY, NATURE PUBLISHING, US, vol. 20, no. 3, March 2002 (2002-03), pages 264-269, XP002256784 ISSN: 1087-0156

D4: WO 03/093478 A (MOLMED SPA; CORTI, ANGELO; CURNIS, FLAVIO) 13 November 2003 (2003-11-13)

D5: HUANG X ET AL: "TUMOR INFARCTION IN MICE BY ANTIBODY-DIRECTED TARGETING OF TISSUE FACTOR TO TUMOR VASCULATURE" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 275, 24 January 1997 (1997-01-24), pages 547-550, XP002071588 ISSN: 0036-8075

D6: VAN VLIET A I ET AL: "Distribution of fibronectin isoforms in human renal disease" JOURNAL OF PATHOLOGY 2001 UNITED KINGDOM, vol. 193, no. 2, 2001, pages 256-262, XP002342603 ISSN: 0022-3417

D7: VITI F ET AL: "Increased binding affinity and valence of recombinant antibody fragments lead to improved targeting of tumoral angiogenesis" CANCER RESEARCH 15 JAN 1999 UNITED STATES, vol. 59, no. 2, 15 January 1999 (1999-01-15), pages 347-352, XP002124782 ISSN: 0008-5472

D8: CARNEMOLLA B ET AL: "A tumor-associated fibronectin isoform generated by alternative splicing of messenger RNA precursors" JOURNAL OF CELL BIOLOGY 1989 UNITED STATES, vol. 108, no. 3, 1989, pages 1139-1148, XP002342604 ISSN: 0021-9525

D9: ZHU Z ET AL: "INHIBITION OF TUMOR GROWTH AND METASTASIS BY TARGETING TUMOR-ASSOCIATED ANGIOGENESIS WITH ANTAGONISTS TO THE RECEPTORS OF VASCULAR ENDOTHELIAL GROWTH FACTOR" INVESTIGATIONAL NEW DRUGS, MARTINUS NIJHOFF PUBLISHERS, BOSTON, US, vol. 17, no. 3, 1999, pages 195-212, XP000940444 ISSN: 0167-6997

D10: PENG L S ET AL: "Mechanism of antitumor activity of a single-chain interleukin-12 IgG3 antibody fusion protein (mscIL-12.her2.IgG3)" JOURNAL OF INTERFERON AND CYTOKINE RESEARCH, vol. 21, no. 9, 2001, pages 709-720, XP002342605 ISSN: 1079-9907

D11: LADELL KRISTIN ET AL: "A combination of plasmid DNAs encoding murine fetal liver kinase 1 extracellular domain, murine interleukin-12, and murine interferon-gamma inducible protein-10 leads to tumor regression and survival in melanoma-bearing mice." JOURNAL OF MOLECULAR MEDICINE (BERLIN), vol. 81, no. 4, April 2003 (2003-04), pages 271-278, XP002342606 ISSN: 0946-2716

D12: DICKERSON ERIN B ET AL: "Development of an IL-12 fusion protein for molecular targeting of tumor vasculature" PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, no. 41, March 2000 (2000-03), page 798, ABSTRACT NO. 5074, XP002342607 & 91ST ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH.; SAN FRANCISCO, CALIFORNIA, USA; APRIL 01-05, 2000 ISSN: 0197-016X

D13: WO 02/02143 A (LEXIGEN PHARMACEUTICALS CORP) 10 January 2002 (2002-01-10)

D14: WO 99/29732 A (LEXIGEN PHARMACEUTICALS CORPORATION) 17 June 1999 (1999-06-17)

D15: MAJEWSKI S ET AL: "INTERLEUKIN-12 INHIBITS ANGIOGENESIS INDUCED BY HUMAN TUMOR CELL LINES IN VIVO"

JOURNAL OF INVESTIGATIVE DERMATOLOGY, NEW YORK, NY, US, vol. 106, no. 5, 1996, pages 1114-1118, XP000949299 ISSN: 0022-202X

2 Invention 1

Document **D1** discloses tumour targeting using the fusion protein of L19 with IL-12
Document **D2** discloses tumour targeting using the fusion protein of L19 with IL-12
Document **D3** discloses a fusion protein of anti-oncofoetal fibronectin with IL-12, and its efficacy in the treatment of tumours. This conjugate seems excluded in claims 1-33, but not in claim 34.
Document **D4** discloses on page 26, line 24 of the table, the combination IL-12 + anti-oncofetal fibronectin is mentioned as one of the preferred combinations.
Document **D5** discloses the targeting of IL-12 to the vasculature using a bispecific antibody. Like in the present application, the result is the infarction of the tumour.
Document **D6** discloses the isoforms of fibronectin targeted by BC-1.
Document **D7** discloses 2 antibodies targeting ED-B: E1 et L19.
Document **D8** discloses the specificity of antibody BC-1.
Document **D9** discloses the use of anti-oncofoetal fibronectin antibodies in the anti-angiogenic treatment of tumours.
Document **D10** discloses the fusion protein of anti-her2 variable region with IL-12, and its anti-cancer effects. The passage on page 715 describes the antiangiogenic effect of the conjugate.
Document **D11** discloses a fusion protein containing IL-12, targeted using the VEGF receptor.
Document **D12** discloses a different way of targeting IL-12 to the vasculature. The resulting effect is, however, the same as in the present application.
Document **D13** discloses the use of a conjugate of IL-12 with a different antibody. It also mentions therapy in combination with other anti-cancer agents.
Document **D14** was cited by the applicant in support of the preparation of the fusion protein. Example 6 describes the Pharmacokinetic Properties of IL-12 Fusion Proteins. The antibody-IL-12 fusion proteins were tested for their pharmacokinetic behaviour following intravenous injection into Balb/c mice. Example 7: Treatment of established colon carcinoma with antibody-IL-12 fusion protein.

Due to its amended wording, present claim 34 is no longer anticipated by the description of the fusion proteins described in each of documents **D1** to **D4**. As a consequence, this claim now meets the requirements of Article 33.2 PCT for novelty.

The fusion proteins defined in present claims 1-33 can be distinguished from the fusion proteins as described in any of **D1** to **D4** by their exact sequence.
The problem to be solved by these different fusion proteins is, again identical: treatment of solid tumours by targeting IL-12 to the neovasculature.
This problem is known to be solved in many ways. Where **D1** to **D4** use the antibody L19 for targeting oncofoetal fibronectin, **D5** uses a bispecific antibody, and **D9** another antibody.
Antibodies targeting other epitopes are also used for targeting IL-12 to tumours. The antibody used in **D10** targets a tumour-specific antigen. In **D11**, VEGF is the target. In **D12**, a small peptide targeting $\alpha_V\beta_3$ is used to bring IL-12 to the vasculature.
Documents **D6** and **D8** describe the antibody BC-1, used in the present application. Like L19, it targets specifically oncofoetal fibronectin. The only difference between documents **D1** to **D4** and the present application is therefore the fact, that the targeting antibody has affinity for a different portion of the same oncofoetal fibronectin.

Throughout the present application, the difference between targeted and non-targeted IL-12 is shown. The present authority can therefore not determine any effect resulting from the different way of targeting the same antigen. The conclusion can therefore only be, that targeting IL-12 to oncofoetal fibronectin does indeed result in more efficient tumour infarction than the use of non-targeted IL-12, but that this result is known from each of **D1** to **D4**.
Moreover, starting from any of **D1** to **D4** as closest prior art, the skilled person would need no inventive skills to replace the antibody part of the fusion protein by BC-1, used in the present application, of which he knows the specificity for oncofoetal fibronectin from **D6** or **D8**, thus arriving at one of the specifically described fusion proteins of the present application.
As a consequence, the specific targeting fusion protein does not meet the requirements of Article 33.3 PCT for inventive step.

Inventions 2 and 3.

Inventions 2 and 3 as defined above relate to a method of preparing the different compounds defined in claims 1-34 (claim 42), and to the different types of products (nucleic acids, expression vector and host cell) necessary for this method (claims 35-41).
Document **D14** was cited by the applicant in support of the preparation of the fusion protein. Example 4 describes the Expression of antibody-IL-12 Fusion Proteins, Example 5 the Expression of Single Chain IL-12 Fusion Proteins.
Due to its general wording, present claim 25 is anticipated by this document.
Present inventions 2 and 3 can be distinguished from the teachings of **D14** by the fact, that the exact sequence used is different. However, it is standard practice for the person skilled in the art to adapt the nucleic acid sequence to the protein (s)he wishes to obtain.
Therefore, present claims 36-41 do not meet the requirement of Article 33.3 PCT for inventive step.

DEPENDENT CLAIMS

The dependent claims do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).

For the assessment of the present claim 47 on the question whether it is it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognise as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII
Certain observations on the international application

Claims 1-50 do not meet the requirements of Article 6 PCT in that the matter for which protection it is sought it is not clearly defined. The claims attempt to define the subject-

matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

Claims 51-52 do not define the matter for which protection is sought in technical terms, and therefore fail to meet the requirements of Article 6 PCT for clarity.

CLAIMS

1. A compound comprising a target specific portion and an effector portion wherein:

(i) the target specific portion comprises or consists of a monoclonal antibody having specificity for oncofoetal fibronectin, or a fragment or variant thereof which retains the binding specificity for oncofoetal fibronectin of the parent monoclonal antibody; and

(ii) the effector portion comprises or consists of interleukin-12, or a functional fragment or variant thereof

characterised in the monoclonal antibody having specificity for oncofoetal fibronectin binds to a region of oncofoetal fibronectin other than the ED-B region.

2. A compound according to Claim 1 wherein the target specific portion is capable of binding to an amino acid sequence present in fibronectin expressed in both fetal and normal adult tissue.

3. A compound according to Claim 1 or 2 wherein the target specific portion is capable of binding an amino acid sequence within the repeat 7 domain of fibronectin.

4. A compound according to any one of Claims 1 to 3 wherein the target specific portion is specific for human oncofoetal fibronectin.

5. A compound according to any one of Claims 1 to 4 wherein the monoclonal antibody having specificity for oncofoetal fibronectin is a BC1 antibody, or an antibody capable of competing with the binding of a BC1 antibody to oncofoetal fibronectin.

6. A compound according to Claim 5 wherein the monoclonal antibody having specificity for oncofoetal fibronectin is a BC1 antibody.

7. A compound according to any one of the preceding claims wherein the monoclonal antibody is a human or humanised antibody.

8. A compound according to Claim 6 or 7 wherein the compound binds to oncofoetal fibronectin more tightly than the parent monoclonal antibody.

9. A compound according to Claim 8 wherein the compound binds to oncofoetal fibronectin more at least 2-fold tighter than the parent monoclonal antibody.

10. A compound according to Claim 8 or 9 wherein the compound binds to oncofoetal fibronectin at least 10-fold tighter than the parent BC1 antibody binds to oncofoetal fibronectin.

11. A compound according to any one of the preceding claims wherein the target specific portion comprises a polypeptide of SEQ ID NO: 1.

12. A compound according to any one of the preceding claims wherein the target specific portion comprises a polypeptide of SEQ ID NO: 2.

13. A compound according to Claim 11 or 12 wherein the target specific portion comprises a polypeptide of SEQ ID NO: 1 and a polypeptide SEQ ID NO: 2.

14. A compound according to any one of the preceding claims wherein the target specific portion comprises or consists of an antigen binding fragment of a monoclonal antibody having specificity for oncofoetal fibronectin.

15. A compound according to Claim 14 wherein the target specific portion comprises or consists of an antigen binding fragment selected from the group consisting of Fab-like molecules, such as Fab and $F(ab')_2$, Fv molecules, disulphide-linked Fv molecules, ScFv molecules and single domain antibodies (dAbs).

16. A compound according to any one of the preceding claims wherein the target specific portion comprises one or more antibody constant regions.

17. A compound according to Claim 16 wherein the one or more antibody constant regions comprises or consists of a CH1 domain.

18. A compound according to any one of the preceding claims further comprising an Fc moiety.

19. A compound according to Claim 18 wherein the Fc moiety is derived from human IgG1.

20. A compound according to any one of the preceding claims wherein the target specific portion comprises or consists of a whole BC1 antibody.

21. A compound according to any one of the preceding claims wherein the effector portion comprises or consists of human interleukin-12, or a functional fragment or variant thereof.

22. A compound according to any one of the preceding claims wherein the effector portion comprises or consists of a single-chain interleukin-12.

23. A compound according to any one of Claim 22 wherein the single chain IL-12 consists of an IL-12p35 domain and an IL-12p40 domain.

24. A compound according to any one of Claim 23 wherein the IL-12p35 domain is conjugated to the IL-12p40 domain by a disulphide bond.

25. A compound according to any one of the preceding claims wherein the compound is a fusion protein.

26. A compound according to any one of the preceding claims wherein the target specific portion is fused to the effector portion.

27. A compound according to Claim 26 comprising an immunoglobulin heavy chain fused to the effector portion.

28. A compound according to Claim 27 wherein the immunoglobulin heavy chain and the effector portion are joined via a mutated linker sequence.

29. A compound according to Claim 28 wherein the linker comprises or consists of the amino acid sequence ATATPGAA (SEQ ID NO. 5).

30. A compound according to any one of the preceding claims wherein the compound comprises a polypeptide of SEQ ID NO:6

31. A compound according to any one of the preceding claims wherein the compound comprises a polypeptide of SEQ ID NO:7.

32. A compound according to Claim 30 and 31 wherein the compound comprises a polypeptide of SEQ ID NO:6 and a polypeptide of SEQ ID NO:7.

33. A compound according to any one of Claims 30 to 32 further comprising a polypeptide of SEQ ID 4 linked by disulphide bond to the polypeptide of SEQ ID NO:6.

34. A fusion protein comprising antibody V regions directed against oncofoetal fibronectin, an Fc moiety, and an interleukin-12 moiety, characterised in that antibody V regions bind to a region of oncofoetal fibronectin other than the ED-B region.

35. A nucleic acid molecule encoding a compound according to any one of Claims 1 to 34, or a target specific portion, effector portion or component polypeptide thereof.

36. A nucleic acid molecule according to Claim 35 wherein the molecule comprises one or more of the nucleotide sequences selected from the groups consisting of SEQ ID NOS: 8 to 10.

37. A nucleic acid molecule according to Claim 36 wherein the molecule comprises the nucleotide sequence of SEQ ID NO: 8.

38. A nucleic acid molecule according to Claim 36 or 37 wherein the molecule comprises the nucleotide sequence of SEQ ID NO: 9.

39. A nucleic acid molecule according to any one of Claims 36 to 38 wherein the molecule comprises the nucleotide sequence of SEQ ID NO: 8 and the nucleotide sequence of SEQ ID NO: 9.

40. An expression vector comprising a nucleic acid molecule according to any one of Claims 35 to 39.

41. A host cell comprising a nucleic acid molecule according to any one of Claims 35 to 39 or a vector according to Claim 40.

42. A method of making a compound according to any one of Claims 1 to 34, or a target specific portion, effector portion or component polypeptide thereof, comprising expressing a nucleic acid molecule according to any one of Claims 35 to 39 in a host cell and isolating the compound, portion or component polypeptide therefrom.

43. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 34 and a pharmaceutically acceptable carrier.

44. A pharmaceutical composition according to Claim 43 wherein the composition is suitable for parenteral administration.

45. A compound according to any one of Claims 1 to 34 for use in medicine.

46. Use of a compound according to any one of Claims 1 to 34 in the preparation of a medicament for treating a patient with cancer.

47. A method of treating a patient with cancer, the method comprising administering a compound according to any one of Claims 1 to 34 to said patient.

48. A use according to Claim 46 or a method according to Claim 47 wherein the mammal is a human.

49. A use according to Claim 46 or a method according to Claim 47 wherein the patient has a solid tumour.

50. A use according to Claim 46 or a method according to Claim 47 wherein the cancer is a glioblastoma.

51. A compound substantially as described herein with reference to the description and figures.

52. A pharmaceutical composition substantially as described herein with reference to the description and figures.